Solvent-free photooxygenation of 5-methoxyoxazoles: stereoselective synthesis of α-amino-α-hydroxy carboxylic acid derivatives

Samir Bondock[a]*, Ehab Abdel Latif[a] and Johann Lex[b]

[a]*Department of Chemistry, Faculty of Science, Mansoura University, ET-31556 Mansoura, Egypt*

[b]*Institute of Organic Chemistry, University of Cologne, Greinst. 4, D-50939 Köln, Germany*

A solvent-free photooxygenation of 5-methoxyoxazoles **1a–j** embedded in porphrin-loaded polystyrene beads as solid support is described and applied for the synthesis of 3*H*-1,2,4-dioxazole derivatives **2a–j**. Acid catalysed hydrolysis of 3*H*-1,2,4-dioxazole derivatives gave α-amino-α-hydroxy carboxylic acid derivatives **3a–j**. The structural elucidation of the new compounds were carried on the basis of spectral and X-ray analyses.

Keywords: α-amino acids, 5-methoxyoxazoles, photooxygenation, 3*H*-1,2,4-dioxazoles, singlet oxygen, solvent-free, polystyrene beads, α-amino α-hydroxy acids

Nonproteinogenic α-alkylated α-amino acids play an important role in natural products and in biological investigations. Because of tetrasubstituted asymmetric carbon atom they possess high stability at the stereogenic centre. They exert a remarkable influence on the formation of peptides into which they are incorporated.[1-4] They can therefore be used for the investigation of enzymatic mechanisms and as enzyme inhibitors. Furthermore, they are interesting building units for the synthesis of natural products.[5-6] Cativiela and Diaz-de-Villegas have reviewed recently stereoselective synthesis of acylic[7] and cyclic[8] quaternary α-amino acids.

A possible photochemical key approach to α-amino-α-hydroxy carboxylic acid derivatives is the photooxygenation of 5-methoxyoxazoles. The reactions of singlet oxygen with organic compounds have had many applications in synthesis.[9] These have been of special interest because of their selectivity, good yields, and the mild conditions employed. From the pioneering work of Wasserman group, oxazoles as substrates for photooxygenation have received great attention, and many applications have been found in the literature.[10-12] We previously reported a new synthetic method for the stereoselective synthesis of *erythro* α-amino-β-hydroxy carboxylic acid derivatives[13,14] and *erythro* β-hydroxy dimethyl aspartates.[15] The key reaction is the cycloaddition of electronically excited carbonyl compounds (aldehydes and α-keto ester, respectively) to 5-methoxyoxazoles. More recently, we have developed "one-pot" synthesis of 4-substituted-3-hydroxy pyridines[16] *via* Diels–Alder reactions of 2,4-dimethyl-5-methoxyoxazoles with different types of dienophiles. In continuing of our work with oxazoles, we plan to explore the synthetic possibility of α-amino-α-hydroxy carboxylic acid derivatives *via* solvent-free photooxygenation of 5-methoxyoxazoles.

It has been recognised in recent years that in spite of the favourable reactivity pattern of $^1O_2$, condensed phase photooxygenation conditions suffer from at least four major drawbacks: (a) the sensitiser dye must be soluble in the respective solvent, thus limiting the dye-solvent combinations which can be used, (b) removal of the dye from the product after the reaction either by chromatography or distillation is often an elaborate process, (c) singlet oxygen has its longest lifetimes in environmentally problematic solvents such as halogenated hydrocarbons, (d) solution purging with pure oxygen is highly problematic for industrial applications and sometimes also for small-scale laboratory syntheses. A global solution to all these problems is desirable in order to make photooxygenation a real green chemical process. In order to meet these requirements, several solutions have been considered. Recently Griesbeck and coworkers have described the use of tetraaryl porphyrin sensitisers embedded in a commercially available polystyrene–divinylbenzene (PS–DVB) copolymer as reaction medium for photooxygenation reaction.[17,18] Our strategy depends on the use of dye non-covalently polymer embedded in confined media where loading and unloading of substrate and product, respectively occur by washing.

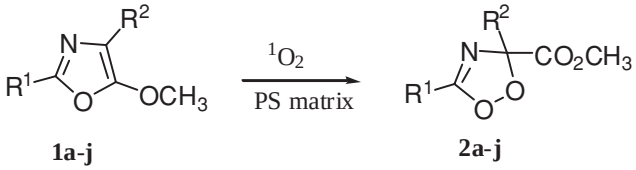
* Correspondent. E-mail: Bondock@mans.edu.eg

Compound	R^1	R^2	Yield/%
2a	Me	H	75
2b	Me	Me	78
2c	Me	Et	85
2d	Me	n-Pr	87
2e	Me	i-Pr	90
2f	Me	i-Br	86
2g	Me	*sec*-Bu	84
2h	Et	Me	92
2i	i-Pr	Me	87
2j	t-Br	Me	85

We used commercially available polystyrene beads (60 ± 15 μm diameter) crosslinked with divinylbenzene as solid support. These beads are known to have easily modifiable space structures which can be controlled by polymer swelling with an appropriate non polar solvent.[19]

The polystyrene beads were loaded with the sensitiser by swelling with a solution of a catalytic amounts *meso*-tetraphenylporphyrin (TPP) in methylene chloride with subsequent evaporation of the excess of solvent. Subsequently, the beads were treated with a solution of 5-methoxy-oxazoles[13,14,20] **1a–j** dissolved in a minimum amount of methylene chloride and by evaporation of the excess transfer solvent, a layer of sandy solid is obtained that was irradiated in a loosely covered Petri dish by means of a sodium street lamp without external cooling or purging with oxygen. After irradiation, the 3*H*-1,2,4-dioxazoles **2a–j** as sole product was isolated from the polymer beads by repeated washing with ethanol in good yields (Scheme 1).

The chemical structures of compounds **2a–j** were established on the basis of rigorous spectroscopic (IR, ^{1}H NMR, ^{13}C NMR, MS) and elemental analyses. The IR spectrum of 3-methoxycarbonyl-5-methyl-*3H*-1,2,4-dioxazole (**2a**)



1a-j **2a-j**

Scheme 1 Solvent-free photooxygenations of 5-methoxyoxazoles **1a–j**.

shows a strong band at 1590 cm^{-1} which was assigned to the –N=C–O ring stretching frequency. This band is shifted to higher frequency when an additional alkyl substituent is introduced to the dioxazole ring in C-3 or C-5 position. In the ^1H NMR spectra of compounds **2a–j**, the methoxy group absorbs at around 3.7 ppm. Their ^{13}C NMR spectra showed two characteristic signals at around 100 and 160 ppm assigned to the C-3 and C-5, respectively.

The lifetime of the excited singlet oxygen in solvent-free photooxygenation process is solely determined by the chemical and physical deactivation induced by the 5-methoxyoxazole itself. The singlet oxygen lifetime has been determined for polystyrene (τ_Δ = 19 s) and resembles that in toluene solution.[21] The *meso*-tetraphenylporphyrin sensitiser, however, is nearly insoluble in the 5-methoxyoxazole substrate which indicates that it is strongly embedded in the polymer matrix with the 5-methoxyoxazole filling the free space. Thus, singlet oxygen is generated by energy transfer probably at the polymer walls and then diffuses into the 5-methoxyoxazole substrate and reacts.

As pictured in Scheme 2, the transformation of 5-methoxyoxazoles **1a–j** to 3*H*-1,2,4-dioxazoles **2a–j** has been rationalised in terms of perepoxide as a type of [1,2]-addition, followed by an intramolecular addition of the peroxidic function to the azomethine group, generating a cyclic peroxide.[22]

From a synthetic point of view, the 3*H*-1,2,4-dioxazoles **2a–j** obtained by the dye-sensitized photooxygenation of 5-methoxyoxazoles **1a–j** in polystyrene beads not only interesting by themselves, but also because they might serve as building blocks for the stereselective construction of α-amino-α-hydroxy carboxylic acid derivatives. Ring opening of the 3*H*-1,2,4-dioxazoles represents the simplest and straight forward strategy for the stereselective synthesis of α-amino-α-hydroxy carboxylic acid derivatives.

Treatment of 3-methoxycarbonyl-5-methyl-*3H*-1,2,4-dioxazole (**2a**) in acetone with 2N hydrochloric acid at room temperature led to the formation of methyl N-acetyl-oxalamate (**3a**) in quantitative yield. The formation of compound **3a** may be rationalised by the autooxidation of non-isolable methyl 2-acetamido-2-hydroxyacetate as depicted in Scheme 3.

The chemical structure of compound **3a** was unambiguously determined by single crystal X-ray analysis as depicted in Fig. 1.

In contrast to the behaviour of compound **2a**, acid hydrolysis of the 3*H*-1,2,4-dioxazoles **2b–j** furnished the quaternary α-amino-α-hydroxy carboxylic acid derivatives **3b–j** in high chemical yields.

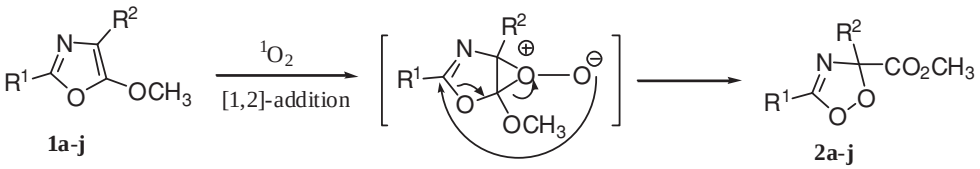
The structural confirmation of compounds **3b–j** was accomplished on the basis of the analytical data and spectroscopic properties. The IR spectra showed absorption bands at around 3455, 3250, 1730 and 1685 cm^{-1} corresponding to the OH, NH, CON and $COOCH_3$ groups, respectively. In the ^{13}C NMR spectra, there is a significant signal at around 83 ppm related to a quaternary carbon. Moreover, the structure determination of both compounds **3b** and **3d** were based on the single crystal X-ray analysis as shown in Fig. 2.

In conclusion, a practical and environmental friendly chemical process for the stereoselective synthesis of α-amino-α-hydroxy carboxylic acid derivatives, which involves the reaction of 5-methoxyoxazoles with singlet oxygen followed by mild acid hydrolysis of the product is developed.

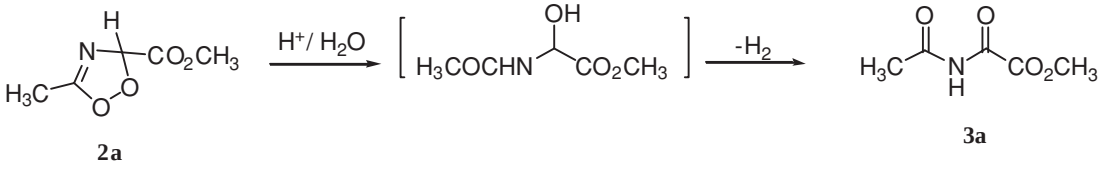
Experimental

All melting points were determined with a Büchi melting point apparatus (type Nr. 535) and are uncorrected. IR spectra were recorded for KBr disc on a Mattson 5000 FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were measured on a Bruker AC 300 (300 MHz) in $CDCl_3$ as solvent, using TMS as an internal standard, and chemical shifts are expressed as δ_{ppm}. Mass spectra were determined on Finnigan Incos 500. Elemental analyses were carried out in the Microanalytical Unit of the Faculty of Science, Cairo University.

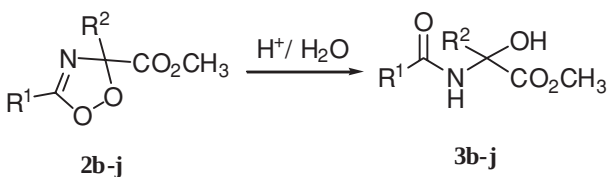
5-Methoxyoxazoles (**1a–j**) were prepared according to reported methods.[13,14,20] TPP (*meso*-tetraphenylporphyrin) was purchased from Porphyrin Systems. Polystyrene beads (1% diviylbenzene copolymer, 100–200 mesh) was purchased by Acros Organics.



Scheme 2 Mechanistic Scenario for the formation of 3*H*-1,2,4-dioxazoles **2a–j**.



Scheme 3 Synthesis of methyl N-acetloxalamate **3a**.



Scheme 4 Synthesis of α-amino-α-hydroxy carboxylic acid derivatives **3b–j**.

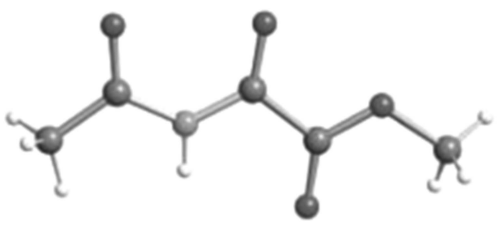


Fig. 1 X-ray structure of compound **3a**.

(3b) **(3d)**

Fig. 2 Single crystal X-ray analysis of compounds **3b** and **3d**.

General procedure for photooxygenation of 5-methoxyoxazoles **1a–j:** A slurry of 2g of polystyrene beads with a solution of 2 mg (3×10^{-3} mmol) of tetraphenylporphyrin and (5 mmol) of 5-methoxyoxazoles in 25 ml of dichloromethane was dispensed on a petri dish (∅19 cm). The excess solvent was evaporated by leaving the petri dish for a few minutes in a well ventilated hood. The sandy solid which was obtained was irradiated for 24 h in the loosely covered Petri dish by a sodium street lamp without external cooling and without external oxygen purging. The polymer beads were subsequently rinsed with 3×20 ml of ethanol and filtered. After evaporation of the solvent, the residue is filtered through a short column of silica gel treated with 1% TEA (eluent pet. ether: ether) to give the pure 1,2,4-dioxazoles. The residual polystyrene beads could be used for three additional photooxygenations; advantageously, ethyl acetate was used instead of dichloromethane for all further photooxygenation reactions.

3-Methoxycarbonyl-5-methyl-3H-1,2,4-dioxazole (**2a**): Colourless oil; yield 0.54 g (75 %); IR (film):ν~ (cm^{-1}) = 2994 (CH-aliph.), 1725 (C=O), 1590 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.50 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 5.42 (s, 1H, CH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 25.2, 54.5, 100.9, 154.4, 170.9; MS: *m/z* = 145 (M^+). Calcd for $C_5H_7NO_4$ (145.11): C, 41.38; H, 4.86, N, 9.65%. Found: C, 41.42; H, 4.89; N, 9.59%.

3,5-Dimethyl-3-methoxycarbonyl-3H-1,2,4-dioxazole (**2b**) Colourless oil; yield 0.62 g (78 %); IR (film):ν~ (cm^{-1}) = 2989 (CH-aliph.), 1720 (CO), 1599 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.66 (s, 3H, CH_3), 2.00 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 9.4, 22.1, 52.8, 106.0, 160.7, 168.4; MS: *m/z* = 159 (M^+). Calcd for $C_6H_9NO_4$ (159.14): C, 45.28; H, 5.07, N, 8.80%. Found: C, 45.32; H, 5.13; N, 8.74%.

3-Ethyl-3-methoxycarbonyl-5-methyl-3H-1,2,4-dioxazole (**2c**): Colourless oil; yield 0.73 g (85 %); IR (film):ν (cm^{-1}) = 2995, 2878 (CH-aliph.), 1716 (CO), 1605 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.91 (t, *J* = 7.5 Hz, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 6.6, 9.5, 28.4, 52.7, 160.7, 168.6; MS: *m/z* = 173 (M^+). Calcd for $C_7H_{11}NO_4$ (173.17): C, 48.55; H, 6.40, N, 8.09%. Found: C, 48.52; H, 6.36; N, 8.17%.

3-Methoxycarbonyl-5-methyl-3-propyl-3H-1,2,4-dioxazole (**2d**): Colourless oil; yield 0.81 g (87 %); IR (film):ν~ (cm^{-1}) = 2992, 2879 (CH-aliph.), 1717 (CO), 1604 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.83 (t, *J* = 7.5 Hz, 3H, CH_3), 1.28 (sextet, *J* = 7.5 Hz, 2H, CH_2), 1.89 (t, *J* = 7.5 Hz, 2H, CH_2), 1.96 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 9.2, 13.6, 15.8, 37.1, 52.7, 108.4, 160.5, 168.6; MS: *m/z* = 187 (M^+). Calcd for $C_8H_{13}NO_4$ (187.19): C, 51.33; H, 7.00, N, 7.48%. Found: C, 51.36; H, 7.11; N, 7.43%.

3-Isopropyl-3-methoxycarbonyl-5-methyl-3H-1,2,4-dioxazole (**2e**): Colourless oil; yield 0.84 g (90 %); IR (film):ν~ (cm^{-1}) = 2982, 2897 (CH-aliph.), 1719 (CO), 1602 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.98 (d, *J* = 7.2 Hz, 3H, $3CH_3$), 1.12 (d, *J* = 7.2 Hz, 3H, CH_3), 1.67 (septet, *J* = 7.2 Hz, 1H, CH), 2.1 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 17.8, 18.4, 19.4, 28.2, 52.3, 108.4, 160.4, 170.8; MS: *m/z* = 187 (M^+). Calcd for $C_8H_{13}NO_4$ (187.19): C, 51.33; H, 7.00, N, 7.48%. Found: C, 51.37; H, 7.17; N, 7.51%.

3-Isobutyl-3-methoxycarbonyl-5-methyl-3H-1,2,4-dioxazole (**2f**): Colourless oil; yield 0.86 g (86 %); IR (film):ν~ (cm^{-1}) = 2975, 2869 (CH-aliph.), 1725 (CO), 1609 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.79 (d, *J* = 6.8 Hz, 3H, CH_3), 0.83 (d, *J* = 6.8 Hz, 3H, CH_3), 1.67 (m, 1H, CH), 1.87 (d, *J* = 5.2 Hz, 2H, CH_2), 1.94 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 9.3, 23.1, 23.2, 23.5, 43.5, 52.6, 108.4, 160.4, 168.7; MS: *m/z* = 201 (M^+). Calcd for $C_9H_{15}NO_4$ (201.22): C, 53.72; H, 7.51, N, 6.96%. Found: C, 53.64; H, 7.59; N, 6.88%.

3-sec-Butyl-3-methoxycarbonyl-5-methyl-3H-1,2,4-dioxazole (**2g**): Colourless oil; yield 0.84 g (84 %); IR (film):ν~ (cm^{-1}) = 2987, 2896 (CH-aliph.), 1714 (CO), 1605 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.81 (d, *J* = 6.8 Hz, 3H, CH_3), 0.84 (t, *J* = 7.4 Hz, 3H, CH_3), 1.09 (m, 2H, CH_2), 1.35 (m, 1H, CH), 1.96 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 9.2, 11.4, 12.1, 22.6, 39.8, 52.5, 111.3, 160.2, 168.8; MS: *m/z* = 201 (M^+). Calcd for $C_9H_{15}NO_4$ (201.22): C, 53.72; H, 7.51, N, 6.96%. Found: C, 53.68; H, 7.48; N, 6.94%.

5-Ethyl-3-methoxycarbonyl-3-methyl-1,2,4-dioxazole (**2h**): Colourless oil; yield 0.79 g (92 %); IR (film):ν~ (cm^{-1}) = 2986, 2868 (CH-aliph.), 1715 (C=O), 1605 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.21 (t, *J* = 7.7 Hz, 3H, CH_3), 1.69 (s, 3H, CH_3), 2.31 (q, *J* = 7.7 Hz, 2H, CH_2), 3.75 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 9.9, 17.5, 22.3, 52.9, 106.1, 164.9, 168.7; MS: *m/z* = 173 (M^+). Calcd for $C_7H_{11}NO_4$ (173.17): C, 48.55; H, 6.40, N, 8.09%. Found: C, 48.52; H, 6.33; N, 7.99%.

5-Isopropyl-3-methoxycarbonyl-3-methyl-3H-1,2,4-dioxazole (**2i**): Colourless oil; yield 0.81 g (87 %); IR (film):ν~ (cm^{-1}) = 2976, 2895 (CH-aliph.), 1716 (CO), 1604 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.03 (s, 3H, CH_3), 1.05 (d, *J* = 7.5 Hz, 3H, CH_3), 1.16 (d, *J* = 7.5 Hz, 3H, CH_3), 1.65 (septet, *J* = 7.5 Hz, 1H, CH), 3.64 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 18.1, 19.2, 19.3, 35.1, 52.2, 107.6, 159.9, 170.9; MS: *m/z* = 187 (M^+). Calcd for $C_8H_{13}NO_4$ (187.19): C, 51.33; H, 7.00, N, 7.48%. Found: C, 51.40; H, 6.96; N, 7.43%.

5-tert-Butyl-3-methoxycarbonyl-3-methyl-3H-1,2,4-dioxazole (**2j**): Colourless oil; yield 0.85 g (85 %); IR (film):ν~ (cm^{-1}) = 2980, 2875 (CH-aliph.), 1714 (CO), 1605 (C=N); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.18 (s, 9H, $3CH_3$), 1.62 (s, 3H, CH_3), 3.69 (s, 3H, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 21.9, 27.6, 52.7, 105.9, 168.6, 169.9; MS: *m/z* = 201 (M^+). Calcd for $C_9H_{15}NO_4$ (201.22): C, 53.72; H, 7.51, N, 6.96%. Found: C, 53.70; H, 7.46; N, 6.91%.

General procedure for the synthesis of α*-amino-*α*-hydroxy carboxylic acid derivatives* **3a–j**: To a solution of the 3*H*-1,2, 4-dioxazole (5 mmol) in 20 ml of acetone, 5 ml of 2N HCl was added. The mixture is stirred in an open flask at room temperature for 3 h and the reaction was controlled by TLC. The reaction mixture was quenched with water and extracted with methylene chloride (3×20 ml). The organic layer was washed with 5 % $NaHCO_3$, brine, and dried over anhydrous $MgSO_4$. The solvent was removed in *vacuo* and the residue was crystallised from ethanol.

Methyl N-acetyloxalamate (**3a**): Colourless needles; yield 0.66 g (92 %); m.p. 92–93°C; IR (KBr):ν~ (cm^{-1}) = 3324 (NH), 2973 (CH-aliph.), 1730 (CO), 1645 (CON), 1635 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 2.48 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 9.23 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 25.1, 54.4, 159.9, 171.0, 171.2; MS: *m/z* = 145 (M^+). Calcd for $C_5H_7NO_4$ (145.11): C, 41.38; H, 4.86, N, 9.65%. Found: C, 41.43; H, 4.35; N, 9.67%.

Methyl 2-acetamido-2-hydroxypropionate (**3b**): White crystals; yield 0.76 g (95 %); m.p. = 114–115°C (Lit.[23] 115–116); IR (KBr): ν~ (cm^{-1}) = 3545 (OH), 3330 (NH), 2965 (CH-aliph.), 1723 (CO), 1645 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.73 (s, 3H, CH_3), 2.00 (s, 1H, OH), 2.05 (s, 3H, CH_3), 3.67 (s, 3H, OCH_3), 7.87 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 18.3, 23.7, 51.3, 76.9, 170.3, 172.0; MS: *m/z* = 161 (M^+). Calcd for $C_6H_{11}NO_4$ (161.16): C, 44.72; H, 6.88, N, 8.69%. Found: C, 44.76; H, 6.82; N, 8.72%.

Methyl 2-acetamido-2-hydroxybutanoate (**3c**): Colourless crystals; yield 0.78 g (90 %); m.p. = 105–106°C; IR (KBr):ν~ (cm^{-1}) = 3560

Table 1 Crystal structure data for compounds **3a**, **3b** and **3d**.

Compound	**3a**	**3b**	**3d**
Emperical formula	$C_5H_7NO_4$	$C_6H_{11}NO_4$	$C_8H_{15}NO_4$
Formula mass	145.12	161.16	189.21
Colour	Colourless	Colourless	Colourless
Temperature (K)	100 (2)	100 (2)	293 (2)
Wavelength(Å)	0.71073	0.71073	0.71073
Size (mm)	0.15 × 0.10 × 0.08	0.15 × 0.15 × 0.10	0.25 × 0.20 × 0.20
a (Å)	3.833 (1)	6.189 (1)	6.163 (1)
b (Å)	10.694 (1)	7.913 (1)	7.834 (1)
c (Å)	7.937 (1)	8.541 (1)	11.184 (1)
α (°)	90	95.40 (1)	95.93 (1)
β (°)	102.98 (1)	94.10 (1)	95.28 (1)
γ (°)	90	107.98 (1)	105.65 (1)
V (Å3)	317.03 (10)	393.85 (9)	513.11 (12)
Z	2	2	2
$d_{calcd.}$ [g/cm^3]	1.520	1.359	1.225
μ [mm $^{-1}$]	0.133	0.114	0.098
Crystal system	Monoclinic	Triclinic	Triclinic
Space group	Pn	P-1	P-1
No. refl. meas.	1057	2614	4338
No. uni. refl.	704	1708	2223
No. obs. refl.[a]	527	1270	1570
R	0.078	0.037	0.044
R_w	0.198	0.056	
Largest diff.			0.069
Peak/hole [e/Å-3]	0.230/–0.253	0.170/–0.168	0.155/–0.197

[a]For I > 2σ (I)

(OH), 3346 (NH), 2986 (CH-aliph.), 1735 (CO), 1635 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.96 (t, *J* = 7.5 Hz, 3H, CH_3), 1.97 (bs, 1H, OH), 2.02 (s, 3H, CH_3), 2.09 (q, *J* = 7.5 Hz, 2H, CH_2), 3.67 (s, 3H, OCH_3), 7.27 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 9.8, 18.7, 35.2, 53.7, 87.1, 170.9, 172.0; MS: *m/z* = 175 (M^+). Calcd for $C_7H_{13}NO_4$ (175.18): C, 47.99; H, 7.48, N, 8.00%. Found: C, 48.07; H, 7.45; N, 7.94%.

Methyl 2-acetamido-2-hydroxypentanoate (**3d**): Colourless crystals; yield 0.91 g (96 %); m.p. = 123–124°C; IR (KBr):ν~ (cm^{-1}) = 3565 (OH), 3329 (NH), 2971 (CH-aliph.), 1738 (CO), 1660 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.91 (t, *J* = 7.4 Hz, 3H, CH_3), 1.27 (m, 1H, CH), 1.46 (m, 1H, CH), 1.78 (m, 2H, CH_2), 1.97 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.82 (bs, 1H, OH), 6.35 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 13.8, 16.3, 22.9, 40.0, 53.2, 82.5, 171.2, 172.2; MS: *m/z* = 189 (M^+). Calcd for $C_8H_{15}NO_4$ (189.21): C, 50.78; H, 7.99, N, 7.40%. Found: C, 50.81; H, 7.92; N, 7.47%.

Methyl 2-acetamido-2-hydroxy-2-methylbutanoate (**3e**): Colourless crystals; yield 0.82 g (87 %); m.p. = 150–151°C; IR (KBr):ν~ (cm^{-1}) = 3553 (OH), 3330 (NH), 2964 (CH-aliph.), 1718 (CO), 1652 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.98 (d, *J* = 7.2 Hz, 3H, CH_3), 1.12 (d, *J* = 7.2 Hz, 3H, CH_3), 1.64 (septet, *J* = 7.2 Hz, 1H, CH), 2.12 (s, 3H, CH_3), 4.62 (s, 1H, OH), 3.77 (s, 3H, OCH_3), 6.49 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 15.7, 17.4, 18.3, 31.3, 53.1, 93.2, 170.1, 172.1; MS: *m/z* = 189 (M^+). Calcd for $C_8H_{15}NO_4$ (189.21): C, 50.78; H, 7.99, N, 7.40%. Found: C, 50.75; H, 8.01; N, 7.46%.

Methyl 2-acetamido-2-hydroxy-4-methylpentanoate (**3f**): Colourless crystals; yield 0.88 g (87 %); m.p. 167–168°C; IR (KBr):ν~ (cm^{-1}) = 3543 (OH), 3334 (NH), 2974 (CH-aliph.), 1716 (CO), 1655 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.01 (d, *J* = 7.4 Hz, 3H, CH_3), 1.21 (d, *J* = 7.4 Hz, 3H, CH_3), 1.83 (m, 1H, CH), 2.02 (s, 3H, CH_3), 3.34 (bs, 1H, OH), 3.82 (s, 3H, OCH_3), 7.37 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 17.2, 18.3, 22.3, 22.4, 43.7, 50.7, 81.4, 170.9, 172.0; MS: *m/z* = 203 (M^+). Calcd for $C_9H_{17}NO_4$ (203.24): C, 53.19; H, 8.43, N, 6.89%. Found: C, 53.21; H, 8.45; N, 6.93%.

Methyl 2-acetamido-2-hydroxy-3-methylpentanoate (**3g**): Colourless crystals; yield 0.91 g (90 %); m.p. 162–163°C; IR (KBr):ν~ (cm^{-1}) = 3538 (OH), 3364 (NH), 2984 (CH-aliph.), 1720 (CO), 1648 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 0.98 (t, *J* = 7.5 Hz, 3H, CH_3), 1.21 (d, *J* = 7.4 Hz, 3H, CH_3), 1.53 (m, 1H, CH), 1.83 (m, 2H, CH_2), 2.12 (s, 3H, CH_3), 3.24 (bs, 1H, OH), 3.79 (s, 3H, OCH_3), 6.49 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 18.2, 19.6, 22.4, 26.6, 43.3, 53.3, 82.4, 170.1, 172.2; MS: *m/z* = 203 (M^+). Calcd for $C_9H_{17}NO_4$ (203.24): C, 53.19; H, 8.43, N, 6.89%. Found: C, 53.25; H, 8.49; N, 6.90%.

Methyl 2-hydroxy-2-(N-propionamido) proponate (**3h**): Colourless crystals; yield 0.82 g (94 %); m.p. 134–135°C; IR (KBr):ν~ (cm^{-1}) = 3543 (OH), 3340 (NH), 2986 (CH-aliph.), 1720 (CO), 1652 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.11 (t, *J* = 7.5 Hz, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.23 (q, *J* = 7.5 Hz, 2H, CH_2), 3.54 (bs, 1H, OH), 3.67 (s, 3H, OCH_3), 6.67 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 16.6, 18.4, 19.4, 39.4, 52.6, 79.8, 170.4, 171.7; MS: *m/z* = 175 (M^+). Calcd for $C_7H_{13}NO_4$ (175.18): C, 47.99; H, 7.48, N, 8.00%. Found: C, 48.05; H, 7.55; N, 7.98%.

Methyl 2-hydroxy-2- (N-isobutyramido) proponate (**3i**): Colourless crystals; yield 0.85 g (90 %); m.p. 112–113°C; IR (KBr):ν~ (cm^{-1}) = 3545 (OH), 3345 (NH), 2994 (CH-aliph.), 1726 (CO), 1645 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.01 (d, *J* = 7.4 Hz, 3H, CH_3), 1.21 (d, *J* = 7.4 Hz, 3H, CH_3), 1.98 (m, 1H, CH), 2.12 (s, 3H, CH_3), 3.32 (bs, 1H, OH), 3.72 (s, 3H, OCH_3), 6.87 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 18.4, 19.4, 20.4, 33.6, 53.3, 81.4, 169.7, 171.1; MS: *m/z* = 189 (M^+). Calcd for $C_8H_{15}NO_4$ (189.21): C, 50.78; H, 7.99, N, 7.40%. Found: C, 50.80; H, 7.95; N, 7.38%.

Methyl 2-hydroxy-2-(N-pivalamido) proponate (**3j**): Colourless crystals; yield 0.90 g (89 %); m.p. 117–118°C; IR (KBr):ν~ (cm^{-1}) = 3540 (OH), 3344 (NH), 2984 (CH-aliph.), 1718 (CO), 1635 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ_{ppm} = 1.19 (s, 9H, $3CH_3$), 2.11 (s, 3H, CH_3), 3.36 (bs, 1H, OH), 3.77 (s, 3H, OCH_3), 6.54 (bs, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ_{ppm} = 19.7, 27.3, 39.4, 52.6, 79.3, 169.8, 170.9; MS: *m/z* = 203 (M^+). Calcd for $C_9H_{17}NO_4$ (203.24): C, 53.19; H, 8.43, N, 6.89%. Found: C, 53.21; H, 8.45; N, 6.93%.

X-ray crystallographic studies:[24] All data sets were collected on a Nonius KappaCCD diffractometer ($2\Theta_{max}$ = 54°, $Mo_{K\alpha}$ radiation (λ = 0.71073 Å), graphite monochromator, φ / ω - scans). No absorption corrections were used. The structures were solved using direct methods (SHELXS-97[25]) , followed by full-matrix least squares refinement (SHELXL-97[26]) with anisotropic thermal parameters for C, N and O and isotropic parameters for H (**3b**, **3d**). The hydrogen atoms in **3a** were calculated and refined as riding atoms. SCHAKAL99[27] was used for the depictions. Crystal structure data and details are listed in Table 1.

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